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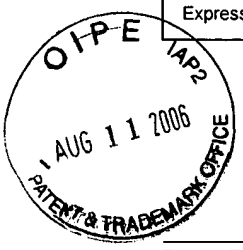

Docket No.: 03818/0204416-US0
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mladen Mercep et al.

Application No.: 10/595,939

Confirmation No.: 9274

Filed: May 19, 2006

Art Unit: N/A

For: 1-AZA-2-OXA-DIBENZO[E,H]AZULENES AND THEIR USE FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISEASES AND DISORDERS

Examiner: Not Yet Assigned

CLAIM FOR PRIORITY AND SUBMISSION OF DOCUMENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby claims priority under 35 U.S.C. 119 based on the following prior foreign application filed in the following foreign country on the date indicated:

Country	Application No.	Date
Croatia	P20030953A	November 21, 2003

In support of this claim, a certified copy of the said original foreign application is filed herewith.

Dated: August 11, 2006

Respectfully submitted,

By (53,970)

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Application No. (if known): 10/595,939 Attorney Docket No.: 03818/0204416-US0

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DRŽAVNI ZAVOD ZA INTELEKTUALNO VLASNIŠTVO

SVJEDODŽBA O PRAVU PRVENSTVA
PRIORITY CERTIFICATE

Državnom zavodu za intelektualno vlasništvo podnesena je prijava patenta s podacima kako slijedi:
The State Intellectual Property Office received the patent application containing the following indications:

(71) Ime(na) podnositelja prijave ili tvrtka i sjedište: */ Name(s) of applicants:*

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(22) Datum podnošenja prijave patenta: */ Date(s) of filing of the application(s):* **21.11.2003.**

(21) Broj prijave patenta: */ Number(s) assigned to the application:* **P20030953A**

(54) Naziv izuma: */ Title of the invention:*

PRIPRAVA 1-AZA-2-OKSA-DIBENZO[e,h]AZULENA I NJIHOVA UPOTREBA ZA PROIZVODNJU FARMACEUTSKIH PRIPRAVAKA ZA TRETIRANJE I PREVENCIJU BOLESTI I POREMEĆAJA SREDIŠNJEG ŽIVČANOG SUSTAVA

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RAVNATELJ
mr.sc. Željko Topić, dipl. oec.

U [illegible] 2.2004.

Kla[illegible]/04-020/0050
Ur. [illegible]-017

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

PREPARATION OF 1-AZA-2-OXA-DIBENZO[*e,h*]AZULENES AND THEIR USE FOR THE MANUFACTURE OF PHARMACEUTICAL FORMULATIONS FOR THE TREATMENT AND PREVENTION OF DISEASES AND DISORDERS OF THE CENTRAL NERVOUS SYSTEM

Disclosure of the Invention

The present invention relates to compounds from the group of 1-aza-2-oxa-dibenzo[*e,h*]azulenes, their pharmacologically acceptable salts and solvates, processes and intermediates for the preparation thereof and to the use thereof for the manufacture of a pharmaceutical formulation for the treatment and prevention of diseases, damages and disorders of the central nervous system (CNS) caused by disorders of the neurochemical equilibrium of biogenic amines.

Prior Art

Irregularities in the steady state of biogenic amines (serotonin, norepinephrine, dopamine) and of other neurotransmitters and their receptors in CNS may be the cause of various mental diseases, damages and disorders (e.g. depression, schizophrenia, manic behaviour and similar). Pathological changes in CNS caused by disorders of neurotransmitter concentration may occur due to an unbalanced (too big or too small) synthesis, irregularities in storing, releasing, metabolizing or reabsorption of a certain neurotransmitter.

The results of investigations directed to the understanding of pathogenesis of mental disorders have shown that a disorder in the serotonin equilibrium plays an important role in various diseases. The monoamine-deficiency hypothesis was one of the first explanations, wherein the symptoms of depression were connected to a reduction in the neurotransmission of monoamines, especially serotonin (5-HT) and noradrenaline,

which was also confirmed by neurochemical tests as well as by a successful treatment of the patients with substances increasing monoaminergic neurotransmission (*Expert Opin. Investig. Drugs* **2003**, 12, 531–543). In addition to the serotonergic and noradrenergic systems, a very important role in CNS function disorders is also played by the dopaminergic system. The understanding of the exact role and of the interactions of these neurotransmitter systems is made rather difficult by the great number of receptor subtypes and their pharmacological complexity. Thus, it has been observed that e.g. dopaminergic neurotransmission is regulated by 5-HT_{2A} receptors (L. G. Spampinato, *J. Neurochem.* **2000**, *74*, 693–701) and hence 5-HT_{2A} receptors may also be the target receptors in treating diseases and disorders, in whose pathology an important role is played by a disorder of the function of the dopaminergic system (psychoses and various addictions).

Pharmacological formulations are most frequently used in the treatment of pathological CNS disorders and a significant place among them as the most frequently applied medicines in the therapy of mental disorders is given to substances that, according to their structure, are polycyclic compounds (benzodiazepines, tricyclic and tetracyclic antidepressants, monoamino oxidase (MAO) inhibitors, selective inhibitors of serotonin reabsorption etc.).

A new area in pharmacotherapy was opened by introducing the novel tetracyclic antidepressant mianserin (Claghorn, J.; Lesem, M. D. *Prog. Drug Res.* **1996**, *46*, 243–262; Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95–102). Numerous tetracyclic derivatives showing pharmacological action in the treatment of the disorders of the neurochemical equilibrium in CNS are disclosed in the literature. WO 99/19317, WO 97/38991 and US 6,511,976 describe the manufacture of tetracyclic derivatives containing tetrahydrofuran ring and the use thereof as substances having antipsychotic, cardiovascular and gastrokinetic actions. US 4,145,434 discloses the manufacture of dibenzo(cyclohepta-, oxepino-, thiepino-)pyrrolidine and dibenzopyrrolidinoazepine derivatives as well as the use thereof as substances having

a potential CNS action. The manufacture and an antidepressive action of some 1,2-diazadibenzoazepines are disclosed in EP 0063525. The manufacture and a potential anxiolytic action of some tetracyclic isooxazolidine derivatives are disclosed as well (*Drugs Fut.* **2002**, 27, Suppl. A: C41; *Drugs Fut.* **2002**, 27, Suppl. A: P182, WO 96/14320, WO 96/14321). The introduction of a piperidine ring into a tetracyclic structure containing an oxepine ring resulted in the formation of the molecule Org-4428 showing an antidepressive action (Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95–102). The molecule Org-5222 contains a pyrrolidine ring fused to an oxepine nucleus and is described as a potential anxiolytic and antipsychotic (Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95–102). Some derivatives of 1,3-diaza-dibenzo[*e,h*]azulenes and salts thereof as a novel class of compounds with antiinflammatory action are known as well (US 3,711,489, US 4,198,421 and CA 967,573).

Derivatives of 1-thia-dibenzo[*e,h*]azulenes with aminoalkyloxy substituents on a thiophene ring and showing an antiinflammatory action were disclosed in WO 01/87890. From the class of 1-thia-dibenzoazulenes, in the literature there are disclosed derivatives substituted in 2-position by methyl, methyl ketone, nitro group or by derivatives of carboxy group (Cagniant PG, *C. R. Hebd. Sceances Acad. Sci.*, **1976**, *283*:683–686) and derivatives of 1-thia-dibenzoazulenes having aminoalkyloxy substituents in 2-position (WO 01/87890) as well as an antiinflammatory action thereof.

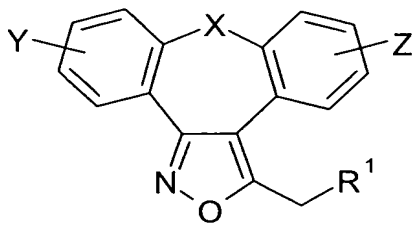
There are also known 2-substituted dibenzoazulenes of tetrahydro pyrazole class with substituents such as acyl alkyloxycarbonyl, phenyl or substituted phenyls (Gansser C. et al., Ann. Pharm. **1984**, *41*: 465–471; or Olivera R. et al., *Tetrahedron Letters*, **2000**, *41*: 4353–4356, 4357–4360). Further, there are known examples of dibenzoazepines of pyrazole and isoxazole class substituted with alkyl (Kawashiha K. Takeda, *Kenkyusho Ho*, **1978**, *37*: 6–11, Fishou D. et al., Tetrahedron **1984**, *40*: 5121–5133), phenyl or substituted phenyl (FR 2,504,140, EP 0063525).

It has been surprisingly found that compounds from the class of 1-aza-2-oxa-dibenzo[*e,h*]azulenes substituted with an aminoalkylether chain are effective in the treatment of diseases and disorders of CNS. If compared with already known tetracyclic compounds acting upon CNS, the compounds of the present invention consist of an unsaturated tetracyclic structure since they contain an isoxazole ring as the fourth ring, whereas the tetracyclic compounds acting upon CNS, which are disclosed in the literature, contain at least one saturated ring in their structure.

According to our knowledge, the use of 1-aza-2-oxa-dibenzo[*e,h*]azulenes and of their pharmaceutically acceptable salts and solvates for the manufacture of a pharmaceutical formulation for the treatment and prevention of diseases, damages and disorders of the central nervous system caused by disorders of neurochemical equilibrium has hitherto been neither disclosed nor suggested.

Solution to the Technical Problem

The present invention relates to the preparation and use of the compounds from the class of 1-aza-2-oxa-dibenzo[*e,h*]azulenes of the general formula **I**:



I

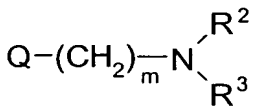
wherein

X means O or S;

Y and Z independently from each other mean one or more identical or different substituents linked to any available carbon atom and may be halogen, hydrogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkinyl, halo-C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy, trifluoromethoxy, C_1-C_4-alkanoyl, amino, amino-C_1-C_4-alkyl, C_1-C_4-alkylamino, *N*-(C_1-C_4-alkyl)amino, *N,N*-di(C_1-C_4-alkyl)amino, thiol, C_1-C_4-alkylthio, sulfonyl, C_1-C_4-alkylsulfonyl, sulfinyl, C_1-C_4-alkylsulfinyl, carboxy, C_1-C_4-alkoxycarbonyl, cyano, nitro;

R^1 may be hydrogen, halogen, optionally substituted C_1-C_7-alkyl or C_2-C_7-alkenyl, C_2-C_7-alkinyl, optionally substituted aryl or heteroaryl and heterocycle, hydroxy, hydroxy-C_2-C_7-alkenyl, hydroxy-C_2-C_7-alkinyl, C_1-C_7-alkoxy, thiol, thio-C_2-C_7-alkenyl, thio-C_2-C_7-alkinyl, C_1-C_7-alkylthio, amino, *N*-(C_1-C_7-alkyl)amino, *N,N*-di(C_1-C_7-alkyl)amino, C_1-C_7-alkylamino, amino-C_2-C_7-alkenyl, amino-C_2-C_7-alkinyl, amino-C_1-C_7-alkoxy, C_1-C_7-alkanoyl, aroyl, oxo-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy, carboxy, optionally substituted (C_1-C_7-alkyloxycarbonyl or aryloxycarbonyl), carbamoyl, *N*-(C_1-C_7-alkyl)carbamoyl, *N,N*-di(C_1-C_7-alkyl)carbamoyl, cyano, cyano-C_1-C_7-alkyl, sulfonyl, C_1-C_7-alkylsulfonyl, sulfinyl, C_1-C_7-alkylsulfinyl, nitro,

or a substituent represented with the formula **II**:



II

wherein

R^2 and R^3 simultaneously or independently from each other may be hydrogen, C_1-C_4-alkyl, aryl or together with N have the meaning of optionally substituted heterocycle or heteroaryl;

m has the meaning of an integer from 1 to 3;

Q has the meaning of oxygen, sulfur or nitrogen;

of their pharmaceutically acceptable salts and solvates for the manufacture of pharmaceutical formulations for the treatment and prevention of diseases, damages and disorders of the central nervous system caused by disorders of neurochemical equilibrium of biogenic amines.

The term "halo", "hal" or "halogen" relates to a halogen atom which may be fluorine, chlorine, bromine or iodine.

The term "alkyl" relates to alkyl groups with the meaning of alkanes wherefrom radicals are derived, which radicals may be straight, branched or cyclic or a combination of straight and cyclic ones and branched and cyclic ones. The preferred straight or branched alkyls are e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, *sec*-butyl and *tert*-butyl. The preferred cyclic alkyls are e.g. cyclopentyl or cyclohexyl.

The term "haloalkyl" relates to alkyl groups which must be substituted with at least one halogen atom. The most frequent haloalkyls are e.g. chloromethyl, dichloromethyl, trifluoromethyl or 1,2-dichloropropyl.

The term "alkenyl" relates to alkenyl groups having the meaning of hydrocarbon radicals, which may be straight, branched or cyclic or are a combination of straight and cyclic ones or branched and cyclic ones, but having at least one carbon-carbon double bond. The most frequent alkenyls are ethenyl, propenyl, butenyl or cyclohexenyl.

The term "alkinyl" relates to alkinyl groups having the meaning of hydrocarbon radicals, which are straight or branched and contain at least one and at most two carbon-carbon triple bonds. The most frequent alkinyls are e.g. ethinyl, propinyl or butinyl.

The term "alkoxy" relates to straight or branched chains of alkoxy group. Examples of such groups are methoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy.

The term "aryl" relates to groups having the meaning of an aromatic ring, e.g. phenyl, as well as to fused aromatic rings. Aryl contains one ring with at least 6 carbon atoms or two rings with totally 10 carbon atoms and with alternating double (resonant) bonds between carbon atoms. The most freqently used aryls are e.g. phenyl or naphthyl. In general, aryl groups may be linked to the rest of the molecule by any available carbon atom via a direct bond or via a C_1-C_4-alkylene group such as methylene or ethylene.

The term "heteroaryl" relates to groups having the meaning of aromatic and partially aromatic groups of a monocyclic or bicyclic ring with 4 to 12 atoms, at least one of them being a hetero atom such as O, S or N, and the available nitrogen atom or carbon atom is the binding site of the group to the rest of the molecule either via a direct bond or via a C_1-C_4-alkylene group defined earlier. Examples of this type are thiophenyl, pyrrolyl, imidazolyl, pyridinyl, oxazolyl, thiazolyl, pyrazolyl, tetrazolyl, pirimidinyl, pyrazinyl, quinolinyl or triazinyl.

The term "heterocycle" relates to five-member or six-member, completely saturated or partly unsaturated heterocyclic groups containing at least one hetero atom such as O, S or N, and the available nitrogen atom or carbon atom is the binding site of the group to the rest of the molecule either via a direct bond or via a C_1-C_4-alkylene group defined earlier. The most frequent examples are morpholinyl, piperidyl, piperazinyl, pyrrolidinyl, pirazinyl or imidazolyl.

The term "alkanoyl" group relates to straight chains of acyl group such as formyl, acetyl or propanoyl.

The term "aroyl" group relates to aromatic acyl groups such as benzoyl.

The term "optionally substituted alkyl" relates to alkyl groups which may be optionally additionally substituted with one, two, three or more substituents. Such substituents may be halogen atom (preferably chlorine or fluorine), hydroxy, C_1-C_4-alkoxy (preferably methoxy or ethoxy), thiol, C_1-C_4-alkylthio (preferably methylthio or ethylthio), amino, *N*-(C_1-C_4-alkyl)amino (preferably *N*-methylamino or *N*-ethylamino), *N,N*-di(C_1-C_4-alkyl)amino (preferably dimethylamino or diethylamino), sulfonyl, C_1-C_4-alkylsulfonyl (preferably methylsulfonyl or ethylsulfonyl), sulfinyl, C_1-C_4-alkylsulfinyl (preferably methylsulfinyl).

The term "optionally substituted alkenyl" relates to alkenyl groups optionally additionally substituted with one, two or three halogen atoms. Such substituents may be e.g. 2-chloroethenyl, 1,2-dichloroethenyl or 2-bromo-propen-1-yl.

The term "optionally substituted aryl, heteroaryl or heterocycle" relates to aryl, heteroaryl or heterocyclic groups which may be optionally additionally substituted with one or two substituents. The substituents may be halogen (preferably chlorine or fluorine), C_1-C_4-alkyl (preferably methyl, ethyl or isopropyl), cyano, nitro, hydroxy, C_1-C_4-alkoxy (preferably methoxy or ethoxy), thiol, C_1-C_4-alkylthio (preferably methylthio or ethylthio), amino, *N*-(C_1-C_4)alkylamino (preferably *N*-methylamino or *N*-ethylamino), *N,N*-di(C_1-C_4-alkyl)amino (preferably *N,N*-dimethylamino or *N,N*-diethylamino), sulfonyl, C_1-C_4-alkylsulfonyl (preferably methylsulfonyl or ethylsulfonyl), sulfinyl, C_1-C_4-alkylsulfinyl (preferably methylsulfinyl).

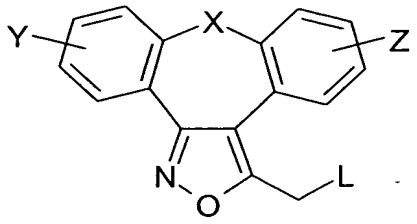
When R^2 and R^3 together with N have the meaning of heteroaryl or heterocycle, this means that such heteroaryls or heterocycles have at least one carbon atom replaced by a nitrogen atom through which the groups are linked to the rest of the molecule. Examples of such groups are morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, imidazol-1-yl or piperazin-1-yl.

The term "pharmaceutically suitable salts" relates to salts of the compounds of the formula **I** and include e.g. salts with C_1-C_4-alkylhalides (preferably methyl bromide, methyl chloride) (quaternary ammonium salts), with inorganic acids (hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric or sulfuric acids) or with organic acids (tartaric, acetic, citric, maleic, lactic, fumaric, benzoic, succinic, methane sulfonic or *p*-toluene sulfonic acids).

The present invention also relates to all possible tautomeric forms of particular compounds of the formula **I**.

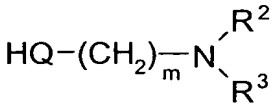
A further object of the present invention relates to the preparation of the compounds of the formula **I** according to the following processes:

a) condensation of compound **Ia**:



Ia

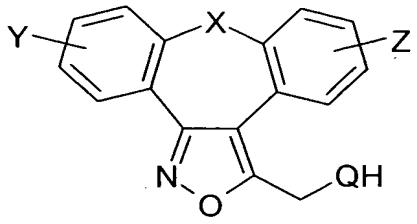
wherein X, Y and Z have the earlier stated meanings, L has the meaning of a leaving group,
with an optionally selected alcohol, thioalcohol or amine or with a compound of the formula **IIa**:



IIa

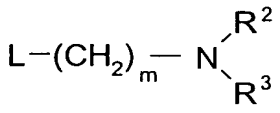
wherein all radicals and symbols have the earlier stated meanings;

b) condensation of compound of the formula **Ib**:



Ib

wherein all symbols have the earlier stated meanings, with a compound of the formula **IIb**:



IIb

wherein radicals R^2 and R^3 and symbol m have the earlier stated meanings and symbol L has the meaning of a good leaving group.

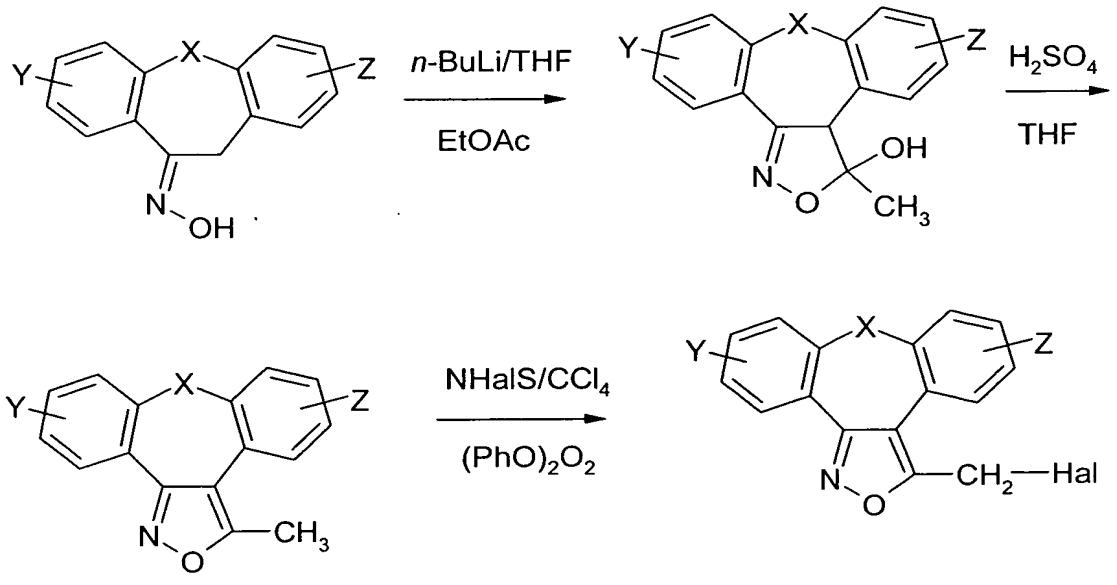
Preparation methods

a) Compounds of the formula **I** according to the present process are prepared by reaction of compounds of the formula **Ia**, wherein L has the meaning of a leaving group, with optionally selected alcohols, thioalcohols or amines, or with compounds of the formula **IIa**, wherein Q has the meaning of oxygen, nitrogen or sulfur. The

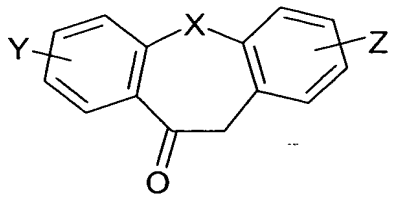
condensation reactions may be carried out most conveniently according to methods disclosed for the preparation of analogous compounds (Menozzi G et al., *J. Heterocyclic Chem.*, **1997**, *34*:963-968 or WO 01/87890). The reactions are carried out at a temperature from 20°C to 100°C during 1 to 24 hours in a two-phase system (preferably with 50% NaOH/toluene), sometimes in the presence of a phase transfer catalyst (preferably benzyl triethyl ammonium chloride, benzyl triethyl ammonium bromide, cetyl trimethyl bromide). After the treatment of the reaction mixture, the products formed are isolated by recrystallization or chromatography on a silica gel column.

The starting compounds of the formula **Ia** (most frequently halides) may be obtained by the reaction sequence represented in Scheme I according to the processes described for analogous compounds (Talley J. J. et al., *J. Med. Chem.*, **2000**, *43*: 775–777).

Scheme I



Hydroxylamines required for the above reaction sequence are compounds known from the literature or are prepared by the action of $NH_2OH \cdot HCl$ upon ketones



in the presence of NaOAc in an alcohol-aqueous medium.

The starting alcohols, thioalcohols or the compounds of the formula **IIa** are commercially available substances or are prepared according to methods disclosed for the preparation of analogous compounds.

b) The compounds of the formula **I** may be prepared according to the present process by condensation of compounds of formula **Ib** with optionally selected halides or with compounds of formula **IIb**, wherein L has the meaning of a leaving group. The condensation reactions are reactions of nucleophilic substitution on saturated carbon atom, which are described in the literature and are carried out in an analogous manner as described in method a).

The starting compounds, alcohols of the formula **Ib,** may be obtained by the action of water, ammonia or hydrogen sulfide upon halides of formula **Ia** in a manner disclosed in the literature. The starting optionally selected halides or compounds of the formula **IIb** are already known or are prepared according to methods disclosed for the preparation of analogous compounds.

Besides the above-mentioned reactions, the compounds of the formula **I** may be prepared by the transformation of other earlier prepared compounds of the formula **I** and it is to be understood that the present invention also comprises such compounds

and processes. An example of such transformation is a reaction of the aldehyde group with chosen phosphorous ylides resulting in a prolongation of the chain and the formation of an alkenyl substituent with carbonyl or ester groups as disclosed in WO 01/87890. These reactions are carried out in solvents such as benzene, toluene or hexane at elevated temperature (most frequently at boiling temperature of the solvent).

A further general example of transformation is formylation of the compounds of the formula **I** by processes such as e.g. Vilsmeier acylation or reaction of *n*-BuLi and dimethylformamide. The reaction conditions of these processes are known in the literature.

By hydrolysis of the compounds of the formula **I** having nitrile, amide or ester groups, there may be prepared compounds with a carboxyl group, which are suitable intermediates for the preparation of other compounds with novel functional groups such as e.g. esters, amides, halides, anhydrides, alcohols or amines.

Oxidation or reduction reactions are a further possibility of the change of substituents in the compounds of the formula **I**. Most frequently used oxidation agents are peroxides (hydrogen peroxide, *m*-chloroperbenzoic acid or benzoyl peroxide) or permanganate, chromate or perchlorate ions. Thus e.g. by the oxidation of an alcohol group by pyridinyl dichromate or pyridinyl chlorochromate, an aldehyde group is formed, which group may be converted to a carboxyl group by further oxidation.

By a selective oxidation of alkylthio group, alkylsulfinyl or alkylsulfonyl groups may be prepared.

By the reduction of the compounds with a nitro group, the preparation of amino compounds is made possible. The reaction is carried out under usual conditions of catalytic hydrogenation or electrochemically. By catalytic hydrogenation using

palladium on carbon, alkenyl substituents may be converted to alkyl ones or nitrile group can be converted to aminoalkyl.

Various substituents of the aromatic structure in the compounds of the formula **I** may be introduced by standard substitution reactions or by usual changes of individual functional groups. Examples of such reactions are aromatic substitutions, alkylations, halogenation, hydroxylation as well as oxidation or reduction of substituents. Reagents and reaction conditions are known from the literature. Thus e.g. by aromatic substitution a nitro group is introduced in the presence of concentrated nitric acid and sulfuric acid. By using acyl halides or alkyl halides, the introduction of an acyl group or an alkyl group is made possible. The reaction is carried out in the presence of Lewis acids such as aluminum- or iron-trichloride in conditions of Friedel-Craft reaction. By the reduction of the nitro group, an amino group is obtained, which is by a diazotizing reaction converted to a suitable starting group, which may be replaced with one of the following groups: H, CN, OH, Hal.

In order to prevent undesired interaction in chemical reactions, it is often necessary to protect certain groups such as e.g. hydroxy, amino, thio or carboxy. For this purpose a great number of protecting groups may be used [Green TW, Wuts PGH, Protective Groups in Organic Synthesis, John Wiley and Sons, 1999)] and the choice, use and elimination thereof are conventional methods in chemical synthesis.

A convenient protection for amino or alkylamino groups are groups such as e.g. alkanoyl (acetyl), alkoxycarbonyl (methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl); arylmethoxycarbonyl (benzyloxycarbonyl), aroyl (benzoyl) or alkylsilyl (trimethylsilyl or trimethylsilylethoxymethyl) groups. The conditions of removing a protecting group depend upon the choice and the characteristics of this group. Thus e.g. acyl groups such as alkanoyl, alkoxycarbonyl or aroyl may be eliminated by hydrolysis in the presence of a base (sodium hydroxide or potassium hydroxide), *tert*-butoxycarbonyl or alkylsilyl (trimethylsilyl) may be eliminated by

treatment with a suitable acid (hydrochloric, sulfuric, phosphoric or trifluoroacetic acid), whereas arylmethoxycarbonyl group (benzyloxycarbonyl) may be eliminated by hydrogenation using a catalyst such as palladium on carbon.

Salts of the compounds of the formula **I** may be prepared by generally known processes such as e.g. by reacting the compounds of the formula **I** with a corresponding base or acid in an appropriate solvent or solvent mixture e.g. ethers (diethylether) or alcohols (ethanol, propanol or isopropanol).

The compounds of the present invention are especially effective in treating those diseases and disorders where the neurochemical equilibrium of biogenic amines such as serotonin, norepinephrine and dopamine was disturbed and which may be caused by unbalanced (too big or too small) synthesis, irregularities in storing, releasing, metabolizing and/or reabsorption of a certain neurotransmitter.

It has been found that the compounds of the present invention exhibit a significant affinity for binding to serotonin receptors, especially to 5-HT_{2A} and 5-HT_{2C}. Preferably, the compounds of the present invention show affinity for binding to 5-HT_{2A} and 5-HT_{2C} serotonin receptors in the concentration $IC_{50}<1\,\mu M$. Since serotonin receptors are crucial in pathophysiology of a series of CNS disorders (directly or indirectly by participating in the activation of some other neurotransmitter e.g. dopamine and/or receptor), the compounds of the present invention may be used for the manufacture of pharmaceutical formulations for the treatment and prevention of diseases, damages and disorders, wherein biogenic amines and their receptors play an important role.

In general, the compounds of the present invention may be used for the manufacture of pharmaceutical formulations that are used as antidepressants, anxiolytics, antipsychotics or as drugs for treating migraine.

Further, the compounds of the present invention may be used for the manufacture of pharmaceutical formulations for the treatment and prevention of diseases and disorders which are the result of disorders of neurochemical equilibrium in the central nervous system such as e.g. depression and modest depression, anxiety, bipolar disorders, sleeping disorders, sexual disorders, psychoses, borderline psychoses, schizophrenia, migraine, personality disorders and obsessive-compulsive disorders, social phobias or panic attacks, organic mental disorders in children, aggression, memory disorders and personality disorders in elderly people, addiction, obesity, bulimia and similar disorders, snoring, premenstrual troubles.

Likewise, these compounds may be used in the treatment and/or prevention of CNS damage caused by trauma, brain stroke, neurodegenerative diseases, cardiovascular disorders such as high blood pressure, thrombosis, infarct and similar diseases as well as in gastrointestinal disorders.

The effective dose of the active substance of the present invention and of a pharmaceutically acceptable salt or solvate thereof depends on the efficacy of the compound of the general formula **I**, on the nature and the severity of the disease and the disorder of CNS as well as on the body weight of the patient treated and may be from 0.001–10 mg/kg body weight. In any case a unit dose for an adult of an average weight of 70 kg is understood to be 0.07–1000 mg of the compound of the general formula **I** or of a pharmaceutically acceptable salt or solvate thereof. A unit dose may be administered once or several times daily, e.g. 2, 3 or 4 times daily, most frequently 1 to 3 times daily.

The present invention more specifically relates to an effective dose of the compounds which bind to serotonin, sigma, adrenergic, dopamine or muscarinic receptors and/or act as inhibitors of reabsorption of one or more biogenic amines (serotonin, dopamine, norepinephrine).

Pharmaceutically acceptable salts relate to salts of hydrobromic, hydrochloric, perchloric, sulfuric, maleic, fumaric, tartaric, citronic, benzoic, mandelic, methanesulfonic, benzenesulfonic, oxalic, p-toluenesulfonic, 2-naphthalenesulfonic and phosphoric acids. Pharmaceutical solvates relate to hydrates, ethanolates and similar.

Further, the present invention relates to a pharmaceutical formulation containing an effective non-toxic dose of the compounds of the present invention as well as pharmaceutically acceptable carriers or solvents.

The pharmaceutical formulations are obtained by blending a therapeutically active amount of a certain substance as the active ingredient with a pharmaceutically acceptable carrier, which may have different forms depending on the desired administration route. These pharmaceutical formulations especially relate to oral, sublingual, rectal, percutaneous or parenteral administration route.

Pharmaceutical formulations may be manufactured using conventional pharmaceutical auxiliaries and manufacture routes. Forms for oral administration may be syrups, capsules, tablets and similar forms where usual solid carriers are inert substances such as lactose, starch, glucose, methylcellulose, magnesium stearate, dicalcium phosphate, mannitol and similar, and usual liquid oral auxiliaries include ethanol, glycerol, water and similar. All auxiliaries may be optionally blended with disintegrants, diluents, granulating agents, wetting agents, binders and similar by using conventional methods. Parenteral forms may be manufactured by using water or some other sterile carrier. When for the manufacture of oral formulations some of the common liquid carriers e.g. water, glycol, oils, alcohols and similar are used, the formulation may be in the form of syrup, emulsion, soft gelatine capsules or sterile injectable liquids e.g. ampoules, or of non-aqueous liquid suspensions. When for the manufacture of oral formulations a solid carrier such as starch, sugar, kaolin, wetting agents, binders, disintegrants and similar is used, the formulation may be in the form of a powder,

capsule, tablet, hard gelatine capsules or granules that may be administered in capsules, and the amount of the solid carrier may vary (most frequently from 1 mg to 1 g). Due to their easy use, tablets and capsules are the most convenient oral formulations wherein a solid carrier is used. For parenteral formulations the carrier is mostly sterile water, though other ingredients may be contained therein as well in order to improve solubility. For the manufacture of injectable solutions, sodium chloride solution, glucose solution or a mixture thereof is used. Injectable solutions may also contain a component for a delayed release of active component. Convenient oils that may be used for this purpose are e.g. arachic oil, sesame oil, cottonseed oil, corn oil, soybean oil, synthetic glycerol esters of long-chain fatty acids or a mixture of some of said oils. Injectable suspensions may be manufactured in such a way that a suitable liquid carrier used is blended with a suspending agent. In formulations convenient for percutaneous administration, as a carrier there is understood a substance improving the penetration of the active substance and/or a suitable wetting agent, which may be combined with a suitable additive of any provenience, which additives do not cause harmful effects on skin. Said additives may facilitate the skin administration and/or may be used in the manufacture of the desired formulations, which may be applied in various ways e.g. transdermally, spot-on, or in the form of an ointment.

To improve the solubility and/or stability of the present compounds, in pharmacological formulations there may be used α-, β- or γ-cyclodextrins or derivatives thereof, especially hydroxyalkyl substituted cyclodextrins i.e. 2-hydroxypropyl-β-cyclodextrin. Cosolvents such as e.g. alcohols may also improve the solubility and/or stability of the present compounds in various pharmaceutical formulations.

The effect of the compounds of the present invention on the neurochemical steady state was determined by *in vitro* investigations such as a radionuclide-marked radioligand binding assay for 5-HT_{2A} (Bonhaus D. W. Br. *J. Pharmacol.* **1995**,

115:622; Saucier C. *J. Neurochem.* **1997,** *68*:1998) and 5-HT_{2C} receptors (Wolf W. A. *J. Neurochem.* **1997**, *69*:1449) and by *in vivo* investigations in a tail suspension test (Vogel H. G. and Vogel W. H. Drug Discovery and Evaluation Pharmacological Assays, Springer **1997,** 304), in a forced swim test in mice (Porsolt R. D. et al. *Arch. Int. Pharmacodyn.* **1977**, *229*:327–336), in meta-chlorophenyl piperazine (m-CPP) test on rats (*Drug Dev. Res.* **1989**, *18*:119–144), and in apomorphine, tryptamine, norepinephrine (ATN) test in rats (*Arch. Int. Pharmacodyn.* **1977**, *227*:238–253).

In *vitro* method for determining affinity for binding to 5-HT_{2A} and 5-HT_{2C} receptors

A small concentration of a radioligand having a great affinity for binding to a receptor was incubated with a tissue sample enriched with a certain receptor (1–5 mg of tissue) in a buffered medium (0.2–5 mL). Recombinant human HT_{2A} and HT_{2C} receptors were expressed in CHO-K1 or COS-7 cells and were also used for competitive binding. During incubation the radioligand bound to the receptor. When a binding balance was achieved, the receptors to which the radioligand was bound were separated from those to which said ligand was not bound, and the radioactivity of the receptor/radioligand complex was measured. The interaction of the tested compounds with receptors was tested in competitive binding experiments. Various concentrations of tested compounds were added to the incubation mixture containing a prepared tissue enriched with corresponding receptors and the radioligand. The radioligand binding was inhibited by the test compounds proportionally to the affinity of a certain compound for the receptor and to the concentration of the compound.

The radioligand used for the determination of binding to 5-HT_{2A} receptor was [^{3}H]-ketanserin and the tissue used was human cortex or recombinant 5-HT_{2A} receptor expressed in CHO-K1.

The radioligand used for the determination of binding to 5-HT_{2C} receptor was [^{3}H]-mesulergine and the tissue used was choroid plexus or recombinant 5-HT_{2C} receptor expressed in CHO-K1 cells.

Compounds showing IC_{50} in concentrations lower than 1 μM, were considered to be active.

Forced swim test in mice

Male CD1 mice of the weight of 20–25 g were used for the experiment. On the day of the experiment the animals were placed into a glass cylinder (height 18.2 cm, diameter 13.3 cm) filled with water warmed to 22 °C to the height of 10 cm. The immobility defined as the end of the struggling of the animal and the beginning of floating, wherein the movements were reduced to those indispensable for the animal to keep its head over the water surface, started to be recorded after two minutes and then it was monitored during 4 minutes. The tested substance was administered *per os* 30 minutes before the test.

The percentage of animals showing a passive behaviour was calculated and compared with a control group treated with a carrier. The compounds that in a dose of 10 mg/kg reduced the immobility of animals for 30 % and more over the control group were considered to be active.

Tail suspension test in mice

Male Balb/cJ mice of the weight of 20–25 g were used for the experiment. The tested substance were administered to the animals 30 minutes before the test. Mice were suspended from their tails at a height of about 90 cm and were observed for 5 minutes.

The mice hanging fully motionless for 1 minute during the observation period were defined as depressive. In animals treated with a substance having an antidepressive action the period of immobility was shortened.

The percentage of animals showing a passive behaviour was calculated and compared with a control group treated with a carrier. The compounds that in a dose of 10 mg/kg reduced the immobility of animals for 40 % and more over a control group were considered to be active.

Meta-chlorophenyl piperazine (m-CPP) test on rats

The tested substance was administered to rats *per os* 1 hour before the test and m-CPP in a dose of 1 mg/kg was administered intravenously 15 minutes before the test. At the beginning of the experiment the treated animals were subjected to an open field test on rats (*Drug Dev. Res.* **1989**, 18, 119–144): the apparatus consisted of an open box having the dimensions 80 × 65 × 35 cm, which in one wall had an opening with a diameter of 10 cm, by which it was connected to a non-illuminated compartment having the dimensions 25 × 21 × 21 cm, and the opening was illuminated by a light source (IR source or Kleverlux®; 12 V/20 W) from the distance of 66 cm; one hour after administering the tested substance, the animals were placed in the dark (non-illuminated) compartment so that their heads were turned away from the illuminated exit and the passing of the animals from the dark compartment to the illuminated one was measured for 10 minutes.

As an active dose of the substance there was defined a dose at which the effect induced by m-CPP was reduced for 40 % and more.

Apomorphine, tryptamine, norepinephrine (ATN) test in rats

At the beginning of the experiment (t = 0) the animals were injected intravenously by 1.25 mg/kg of apomorphine, then by 40 mg/kg of tryptamine (t = 60 minutes) and by 1.25 mg/kg of norepinephrine (t = 90 minutes).

There were watched a state of exceptional agitation and normal behaviour during 60 minutes (apomorphine test), then bilateral clonic convulsions of back paws and a general tremor of the body in tryptamine test (observation period 5 minutes) and lethality during 120 minutes after the injection in norepinephrine test.

The percentage of animals showing a passive behaviour was calculated and compared with a control group treated with a carrier.

The compounds which in a dose of 10 mg/kg reduced the period of duration of observed effects (mobility) for 40 % over a control group were considered to be active in *in vivo* testings.

Some of the present compounds tested in the above assays showed an action in at least two of said tests, though these results represent only an illustration of the biological action of the compounds and do not limit the present invention in any way.

PREPARATION PROCESSES WITH EXAMPLES

The present invention is illustrated by the following Examples which are in no way a limitation thereof.

Example 1

3-Methyl-3,3a-dihydro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ol* (**1a**)

To a solution of 11H-dibenzo[*b,f*]thiepin-10-one oxime (1.66 mmole) in dry THF (10 mL) cooled to –78 °C, n-butyl lithium (3.57 mmole) was slowly added drop by drop. The reaction mixture was stirred for 15 minutes at this temperature, whereupon it was heated to 0 °C and ethyl acetate (3.57 mmole) was added thereto. The stirring of the reaction mixture was continued for 1 more hour at room temperature, whereupon water was added and it was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

^{1}H NMR (ppm, $CDCl_3$): 2.03 (s, 3H), 7.27-7.60 (m, 8H);

MS (*m/z*): 306.1 [MNa^+], 338.1 [MNa^+ + MeOH].

3-Methyl-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulene* (**1**)

To a solution of 3-methyl-3,3a-dihydro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulen-3-ol (**1a**) (0.07 mmole) in THF (5 mL), concentrated sulfuric acid (100 μL) was added. The reaction mixture was stirred and heated under reflux for 5 hours, then it was cooled and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, an oily product was isolated;

^{1}H NMR (ppm, $CDCl_3$): 2.74 (s, 3H), 7.35-7.93 (m, 8H);

MS (*m/z*): 265.9 [MH^+].

Example 2

3-Methyl-3,3a-dihydro-11-chloro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ol* (2**a**)

To a solution of 11-chloro-11H-dibenzo[*b,f*]thiepin-10-one oxime (1.89 mmole) in dry THF (10 mL) cooled to –78 °C, n-butyl lithium (4.07 mmole) was slowly added drop by drop. The reaction mixture was stirred for 15 minutes at this temperature, whereupon it was heated to 0 °C and ethyl acetate (4.07 mmole) was added thereto. The stirring of the reaction mixture was continued for 1 more hour at room temperature, whereupon water was added and it was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 340.1 [MNa^+].

3-Methyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulene* (**2**)

To a solution of 3-methyl-3,3a-dihydro-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulen-3-ol (2**a**) (0.08 mmole) in THF (5 mL), concentrated sulfuric acid (114 μL) was added. The reaction mixture was stirred and heated under reflux for 5 hours, then it was cooled and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, an oily product was isolated;

MS (*m/z*): 300.78 [MH^+].

Example 3

3-Methyl-3,3a-dihydro-2,8-dioxa-1-aza-dibenzo[e,h]*azulen-3-ol* (**3a**)

To a solution of 11H-dibenzo[*b,f*]oxepin-10-one oxime (1.91 mmole) in dry THF (10 mL) cooled to –78 °C, n-butyl lithium (4.10 mmole) was slowly added drop by drop. The reaction mixture was stirred for 15 minutes at this temperature, whereupon it was heated to 0 °C and ethyl acetate (4.10 mmole) was added. The stirring of the reaction mixture was continued for one more hour at room temperature, whereupon water was

added thereto and it was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 290.3 [MNa^+].

3-Methyl-2,8-dioxa-1-aza-dibenzo[e,h]*azulene* (**3**)

To a solution of 3-methyl-3,3a-dihydro-2,8-dioxa-1-aza-dibenzo[*e,h*]azulen-3-ol (**3a**) (0.1 mmole) in THF (7 mL), concentrated sulfuric acid (143 μL) was added. The reaction mixture was stirred and heated under the reflux for 5 hours, then it was cooled and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, an oily product was isolated;

MS (*m/z*): 250.27 [MH^+].

Example 4

1-Bromomethyl-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulene* (**4**)

To a solution of 3-methyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**1**) (0.68 mmole) in carbon tetrachloride (15 mL), NBS (N-bromosuccinimide) (1.02 mmole) and a catalytic amount of benzoyl peroxide $(PhCO)_2O_2$ were added. The reaction mixture was stirred and heated under the reflux for 6–8 hours, then it was cooled, the precipitated succinimide was filtered and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, an oily product was isolated;

^1H NMR (ppm, $CDCl_3$): 4.63 (s, 2H), 7.38-8.10 (m, 8H);

MS (*m/z*): 264.0 [M-Br].

Example 5

1-Bromomethyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulene* (**5**)

To a solution of 3-methyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**2**) (0.78 mmole) in carbon tetrachloride (15 mL), NBS (N-bromosuccinimide) (1.17 mmole) and a catalytic amount of benzoyl peroxide $(PhCO)_2O_2$ were added. The reaction mixture was stirred and heated under reflux for 6–8 hours, then it was cooled, the precipitated succinimide was filtered and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 298.45 [M-Br].

Example 6

1-bromomethyl-2,8-dioxa-1-aza-dibenzo[e,h]*azulene* (**6**)

To a solution of 3-methyl-2,8-dioxa-1-aza-dibenzo[*e,h*]azulene (**3**) (0.58 mmole) in carbon tetrachloride (15 mL), NBS (N-bromosuccinimide) (0.87 mmole) and a catalytic amount of benzoyl peroxide $(PhCO)_2O_2$ were added. The reaction mixture was stirred and heated under reflux for 6–8 hours and cooled, the precipitated succinimide was filtered and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 248.0 [M-Br].

Example 7

Dimethyl-[3-(2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-propyl]-amine* (**7**)

To a solution of 3-dimethylaminopropylchloride-hydrochloride (2.16 mmole) in 50 % sodium hydroxide (1.9 mL), a catalytic amount of benzyltriethylammonium chloride

and a solution of 1-bromomethyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**4**) (0.15 mmole) in toluene (10 mL) were added. The reaction mixture was heated under vigorous stirring and reflux for 3 hours, then it was cooled to room temperature, diluted with water and extracted with dichloromethane. The organic extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 367.2 [MH^+].

Example 8

Dimethyl-[2-(2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-ethyl]-amine* (**8**)

According to the process described in Example 7, starting from 1-bromomethyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**4**) (0.20 mmole) and 2-dimethylamino-ethylchloride-hydrochloride (2.85 mmole), an oily product was obtained;

^1H NMR (ppm, $CDCl_3$): 2.39 (s, 6H), 2.69-2.72 (t, 2H), 3.83-3.87 (t, 2H), 4.79 (s, 2H), 7.35-7.89 (m, 8H);

MS (*m/z*): 353.2 [MH^+], 375.2 [MNa^+].

Example 9

Dimethyl-[2-(11-chloro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-ethyl]-amine* (**9**)

According to the process described in Example 7, starting from 1-bromomethyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**5**) (0.18 mmole) and 2-dimethylaminoethylchloride-hydrochloride (2.56 mmole), an oily product was obtained;

MS (*m/z*): 387.65 [MH^+].

Example 10

Dimethyl-[3-(11-chloro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-propyl]-amine* (**10**)

According to the process described in Example 7, starting from 1-bromomethyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**5**) (0.18 mmole) and 2-dimethylaminopropylchloride-hydrochloride (2.56 mmole), an oily product was obtained;

MS (*m/z*): 401.65 [MH^+].

Example 11

Dimethyl-[2-(2,8-dioxa-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-ethyl]-amine* (**11**)

According to the process described in Example 7, starting from 1-bromomethyl-2,8-dioxa-1-aza-dibenzo[*e,h*]azulene (**6**) (0.25 mmole) and 2-dimethylamino-ethylchloride-hydrochloride (3.42 mmole), an oily product was obtained;

MS (*m/z*): 337.2 [MH^+].

Example 12

Dimethyl-[3-(2,8-dioxa-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-propyl]-amine* (**12**)

According to the process described in Example 7, starting from 1-bromomethyl-2,8-dioxa-1-aza-dibenzo[*e,h*]azulene (**6**) (0.25 mmole) and 2-dimethylamino-propylchloride-hydrochloride (3.42 mmole), an oily product was obtained;

MS (*m/z*): 351.2 [MH^+].

PREPARATION OF STARTING COMPOUNDS

11H-dibenzo[b,f]*thiepin-10-one oxime*

11H-dibenzo[*b,f*]thiepin-10-one (2.21 mmole) was dissolved in absolute ethanol (4.26 mL) and water (1.28 mL) under stirring and gentle heating. To the solution of ketone, aminehydroxide hydrochloride (4.42 mmole) and sodium acetate (4.42 mmole) were

added. The reaction mixture was stirred and heated under reflux for 2 hours. After the completion of the reaction, 30 % ethanol (2 mL) was added into the hot reaction mixture and it was left to cool to room temperature. If no precipitation occurred, the solvent was evaporated under reduced pressure and the residue after evaporation was dissolved in water, extracted with dichloromethane, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

^{1}H NMR (ppm, $CDCl_3$): 3.65 (bs, 1H), 4.34 (s, 2H), 7.18-8.06 (m, 8H);

MS (*m/z*): 242.0 [MH^+], 264.0 [MNa^+], 296.0 [MNa^+ + MeOH].

8-chloro-11H-dibenzo[b,f]*thiepin-10-one oxime*

11-chloro-11H-dibenzo[*b,f*]thiepin-10-one (1,47 mmole) was dissolved in absolute ethanol (2.84 mL) and water (0.9 mL) under stirring and gentle heating. To the solution of ketone, aminehydroxide hydrochloride (2.95 mmole) and sodium acetate (2.95 mmole) were added. The reaction mixture was stirred and heated under reflux for 2 hours. After the completion of the reaction, 30 % ethanol (1 mL) was added into the hot reaction mixture and it was left to cool to room temperature. If no precipitation occurred, the solvent was evaporated under reduced pressure and the residue after evaporation was dissolved in water, extracted with dichloromethane, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 276.45 [MH^+].

11H-Dibenzo[b,f]*oxepin-10-one oxime*

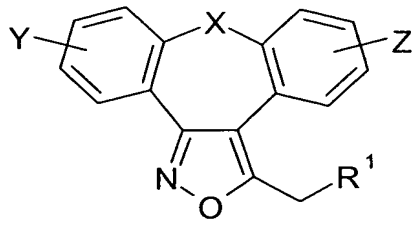
11H-dibenzo[*b,f*]oxepin-10-one (4.42 mmole) was dissolved in absolute ethanol (8.52 mL) and water (2.56 mL) under stirring and gentle heating. To the solution of ketone, aminehydroxide hydrochloride (8.84 mmole) and sodium acetate (8.84 mmole) were added. The reaction mixture was stirred and heated under reflux for 2 hours. After the completion of the reaction, 30 % ethanol (4 mL) was added into the hot reaction mixture and it was left to cool to room temperature. If no precipitation occurred, the

solvent was evaporated under reduced pressure and the residue after evaporation was dissolved in water, extracted with dichloromethane, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 226.0 [MH^+].

CLAIMS

1. Use of the compounds of the general formula **I:**



I

wherein

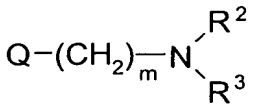
X means O or S;

Y and Z independently from each other mean one or more identical or different substituents linked to any available carbon atom and may be halogen, hydrogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkinyl, halo-C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy, trifluoromethoxy, C_1-C_4-alkanoyl, amino, amino-C_1-C_4-alkyl, C_1-C_4-alkylamino, *N*-(C_1-C_4-alkyl)amino, *N,N*-di(C_1-C_4-alkyl)amino, thiol, C_1-C_4-alkylthio, sulfonyl, C_1-C_4-alkylsulfonyl, sulfinyl, C_1-C_4-alkylsulfinyl, carboxy, C_1-C_4-alkoxycarbonyl, cyano, nitro;

R^1 may be hydrogen, halogen, optionally substituted C_1-C_7-alkyl or C_2-C_7-alkenyl, C_2-C_7-alkinyl, optionally substituted aryl or heteroaryl and heterocycle, hydroxy, hydroxy-C_2-C_7-alkenyl, hydroxy-C_2-C_7-alkinyl, C_1-C_7-alkoxy, thiol, thio-C_2-C_7-alkenyl, thio-C_2-C_7-alkinyl, C_1-C_7-alkylthio, amino, *N*-(C_1-C_7-alkyl)amino, *N,N*-di(C_1-C_7-alkyl)amino, C_1-C_7-alkylamino, amino-C_2-C_7-alkenyl, amino-C_2-C_7-alkinyl, amino-C_1-C_7-alkoxy, C_1-C_7-alkanoyl, aroyl, oxo-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy, carboxy, optionally substituted (C_1-C_7-alkyloxycarbonyl or aryloxycarbonyl), carbamoyl, *N*-(C_1-C_7-alkyl)carbamoyl,

N,N-di(C_1-C_7-alkyl)carbamoyl, cyano, cyano-C_1-C_7-alkyl, sulfonyl, C_1-C_7-alkylsulfonyl, sulfinyl, C_1-C_7-alkylsulfinyl, nitro,

or a substituent represented with the formula **II**:



II

wherein

R^2 and R^3 simultaneously or independently from each other may be hydrogen, C_1-C_4-alkyl, aryl or together with N have the meaning of optionally substituted heterocycle or heteroaryl;

m has the meaning of an integer from 1 to 3;

Q has the meaning of oxygen, sulfur or nitrogen;

of their pharmaceutically acceptable salts and solvates for the manufacture of pharmaceutical formulations useful for the treatment and prevention of diseases, damages and disorders of the central nervous system caused by disorders of neurochemical equilibrium of biogenic amines.

2. Use according to claim 1, wherein the selected biogenic amines are serotonin, norepinephrine and dopamine.

3. Use according to claim 1, wherein the compounds of the general formula **I** act upon the neurochemical equilibrium by regulating the synthesis, storing, releasing, metabolizing and/or reabsorption of biogenic amines.

4. Use according to claim 3, wherein the compounds of the general formula **I** have an affinity for binding to a receptor of one or more biogenic amines.

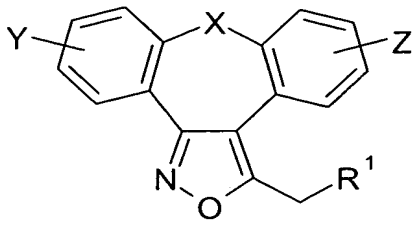
5. Use according to claim 4, wherein the compounds of the general formula **I** have a significant affinity for binding to serotonin 5-HT_{2A} and 5-HT_{2C} receptors.

6. Use according to claim 5, wherein the compounds of the general formula **I** have an affinity for binding to selected serotonin receptors in a concentration of IC50<1μM.

7. Use according to claim 1, wherein the diseases and disorders of the central nervous system are selected from the group consisting of anxiety, depression and modest depression, bipolar disorders, sleeping disorders, sexual disorders, psychosis, borderline psychosis, schizophrenia, migraine, personality disorders and obsessive-compulsive disorders, social phobia or panic attacks, organic mental disorders in children, aggression, memory disorders and personality disorders in elderly people, addiction, obesity, bulimia and similar disorders, snoring, premenstrual troubles.

8. Use according to claim 1, wherein the damages of the central nervous system are caused by trauma, brain stroke, neurodegenerative diseases, cardiovascular disorders such as high blood pressure, thrombosis, infarct as well as by gastrointestinal disorders.

9. Compound of the general formula **I**:



I

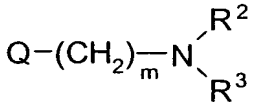
wherein

X means O or S;

Y and Z independently from each other mean one or more identical or different substituents linked to any available carbon atom and may be halogen, hydrogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkinyl, halo-C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy, trifluoromethoxy, C_1-C_4-alkanoyl, amino, amino-C_1-C_4-alkyl, C_1-C_4-alkylamino, *N*-(C_1-C_4-alkyl)amino, *N,N*-di(C_1-C_4-alkyl)amino, thiol, C_1-C_4-alkylthio, sulfonyl, C_1-C_4-alkylsulfonyl, sulfinyl, C_1-C_4-alkylsulfinyl, carboxy, C_1-C_4-alkoxycarbonyl, cyano, nitro;

R^1 may be hydrogen, halogen, optionally substituted C_1-C_7-alkyl or C_2-C_7-alkenyl, C_2-C_7-alkinyl, optionally substituted aryl or heteroaryl and heterocycle, hydroxy, hydroxy-C_2-C_7-alkenyl, hydroxy-C_2-C_7-alkinyl, C_1-C_7-alkoxy, thiol, thio-C_2-C_7-alkenyl, thio-C_2-C_7-alkinyl, C_1-C_7-alkylthio, amino, *N*-(C_1-C_7-alkyl)amino, *N,N*-di(C_1-C_7-alkyl)amino, C_1-C_7-alkylamino, amino-C_2-C_7-alkenyl, amino-C_2-C_7-alkinyl, amino-C_1-C_7-alkoxy, C_1-C_7-alkanoyl, aroyl, oxo-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy, carboxy, optionally substituted (C_1-C_7-alkyloxycarbonyl or aryloxycarbonyl), carbamoyl, *N*-(C_1-C_7-alkyl)carbamoyl, *N,N*-di(C_1-C_7-alkyl)carbamoyl, cyano, cyano-C_1-C_7-alkyl, sulfonyl, C_1-C_7-alkylsulfonyl, sulfinyl, C_1-C_7-alkylsulfinyl, nitro,

or a substituent represented with the formula **II**:



II

wherein

R^2 and R^3 simultaneously or independently from each other may be hydrogen, C_1-C_4-alkyl, aryl or together with N have the meaning of optionally substituted heterocycle or heteroaryl;

m has the meaning of an integer from 1 to 3 and

Q has the meaning of oxygen, sulfur or nitrogen;

and its pharmaceutically acceptable salts and solvates for the manufacture of pharmaceutical formulations.

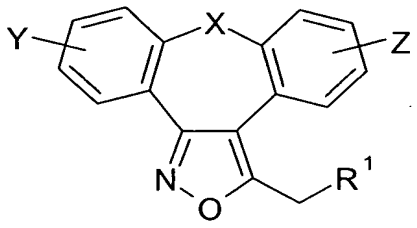
10. Compound according to claim 9, wherein Y has the meaning of H or Cl and Z has the meaning of H.

11. Compound according to claim 10, wherein R^1 has the meaning of CH_3, CH_2Br or CH_2OH.

12. Compound and salt according to claim 10, wherein R^1 has the meaning of formula **II**.

13. Compound and salt according to claim 12, wherein symbol m has the meaning of 2 or 3.

14. Process for the preparation of the compound of the formula **I**:



I

wherein

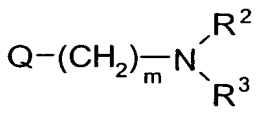
X means O or S;

Y and Z independently from each other mean one or more identical or different substituents linked to any available carbon atom and may be halogen, hydrogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkinyl, halo-C_1-C_4-alkyl,

hydroxy, C_1-C_4-alkoxy, trifluoromethoxy, C_1-C_4-alkanoyl, amino, amino-C_1-C_4-alkyl, C_1-C_4-alkylamino, *N*-(C_1-C_4-alkyl)amino, *N,N*-di(C_1-C_4-alkyl)amino, thiol, C_1-C_4-alkylthio, sulfonyl, C_1-C_4-alkylsulfonyl, sulfinyl, C_1-C_4-alkylsulfinyl, carboxy, C_1-C_4-alkoxycarbonyl, cyano, nitro;

R^1 may be hydrogen, halogen, optionally substituted C_1-C_7-alkyl or C_2-C_7-alkenyl, C_2-C_7-alkinyl, optionally substituted aryl or heteroaryl and heterocycle, hydroxy, hydroxy-C_2-C_7-alkenyl, hydroxy-C_2-C_7-alkinyl, C_1-C_7-alkoxy, thiol, thio-C_2-C_7-alkenyl, thio-C_2-C_7-alkinyl, C_1-C_7-alkylthio, amino, *N*-(C_1-C_7-alkyl)amino, *N,N*-di(C_1-C_7-alkyl)amino, C_1-C_7-alkylamino, amino-C_2-C_7-alkenyl, amino-C_2-C_7-alkinyl, amino-C_1-C_7-alkoxy, C_1-C_7-alkanoyl, aroyl, oxo-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy, carboxy, optionally substituted (C_1-C_7-alkyloxycarbonyl or aryloxycarbonyl), carbamoyl, *N*-(C_1-C_7-alkyl)carbamoyl, *N,N*-di(C_1-C_7-alkyl)carbamoyl, cyano, cyano-C_1-C_7-alkyl, sulfonyl, C_1-C_7-alkylsulfonyl, sulfinyl, C_1-C_7-alkylsulfinyl, nitro,

or a substituent represented with the formula **II**:



II

wherein

R^2 and R^3 simultaneously or independently from each other may be hydrogen, C_1-C_4-alkyl, aryl or together with N have the meaning of optionally substituted heterocycle or heteroaryl;

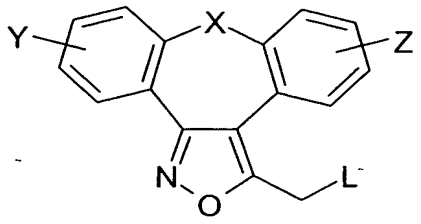
m has the meaning of an integer from 1 to 3 and

Q has the meaning of oxygen, sulfur or nitrogen;

and its pharmacologically acceptable salts and solvates,

comprising:

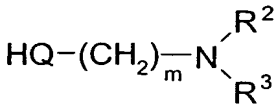
a) condensation of a compound **Ia**:



Ia

wherein symbols X, Y and Z have the earlier stated meanings, L has the meaning of a leaving group,

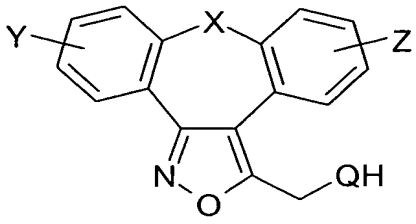
with an optionally selected alcohol, thioalcohol or amine or with a compound of the formula **IIa**:



IIa

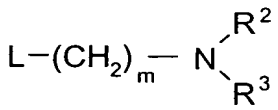
wherein all radicals and symbols have earlier stated meanings;

b) condensation of a compound of the formula **Ib**:



Ib

wherein all symbols have the earlier stated meanings, with a compound of the formula **IIb**:



IIb

wherein the radicals R^2 and R^3 and the symbol m have the earlier stated meanings and symbol L has the meaning of a good leaving group.

15. Use of the compounds of the formula **I** according to claim 11, wherein the compounds are used as intermediates for the preparation of pharmaceutical formulations of 1-aza-2-oxa-dibenzo[*e,h*]azulene class, their pharmacologically acceptable salts and solvates useful for the manufacture of a pharmaceutical formulation for the treatment and prevention of diseases, damages and disorders of the central nervous system caused by disorders of the neurochemical equilibrium of biogenic amines.

16. Use according to claim 1, wherein the compounds of the general formula **I**, pharmaceutically acceptable salts and solvates thereof are selected from the group consisting of:

3-methyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene;

11-chloro-3-methyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene;

3-methyl-2,8-dioxa-1-aza-dibenzo[*e,h*]azulene;

3-bromomethyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene;

3-bromomethyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene;

3-bromomethyl-2,8-dioxa-1-aza-dibenzo[*e,h*]azulene;

dimethyl-[2-(2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulen-3-ylmethoxy)-ethyl]-amine;

dimethyl-[3-(2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulen-3-ylmethoxy)-propyl]-amine;

dimethyl-[2-(11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulen-3-ylmethoxy)-ethyl]-amine;

dimethyl-[3-(11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulen-3-ylmethoxy)-propyl]-amine;

dimethyl-[2-(2,8-dioxa-1-aza-dibenzo[*e,h*]azulen-3-ylmethoxy)-ethyl]-amine;

dimethyl-[3-(2,8-dioxa-1-aza-dibenzo[*e,h*]azulen-3-ylmethoxy)-propyl]-amine.

ABSTRACT

The present invention relates to compounds from the group of 1-aza-2-oxa-dibenzo[*e,h*]azulenes, their pharmacologically acceptable salts and solvates, processes and intermediates for the preparation thereof and to the use thereof for the manufacture of pharmaceutical formulations for the treatment and prevention of diseases, damages and disorders of the central nervous system (CNS) caused by disorders of the neurochemical equilibrium of biogenic amines.